Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
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You should submit comments and suggestions regarding this draft guidance document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov . Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Dr. Charles Durfor at 301-796-6970 (charles.durfor@fda.hhs.gov) or Dr. Scott McNamee at 301-796-5523 or 301-796-5500 (scott.mcnamee@fda.hhs.gov).

This document, when final, will supersede "Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)" issued November 6, 1998.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Transmissible Spongiform Encephalopathy Working Group
Office of Compliance
Office of Device Evaluation

Preface

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Contains Nonbinding Recommendations

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Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices) Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The Food and Drug Administration (FDA) is issuing this draft guidance to update the policy regarding the use of animal-derived material in medical device manufacturing. The role of animal derived-material in medical devices is well established. However, these materials may carry a risk of transmitting infectious disease when improperly collected, stored or manufactured. The guidance describes the information you should document at the manufacturing facility and include in any premarket submissions. This guidance, when finalized, will supersede "Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)" issued November 6, 1998 (the 1998 guidance).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

This draft guidance updates the 1998 guidance by addressing aspects of potential risk from the use of animal tissues (e.g., viruses and bacteria) and now includes recommendations

related to all transmissible spongiform encephalopathies (TSEs). The 1998 guidance addressed ways to reduce the potential for exposure to bovine spongiform encephalopathy (BSE). This document continues to focus on the control of transmissible disease, and contains recommendations for documenting the source of animal tissue and conducting viral inactivation validation studies. Commercial production of animals as the source of animal tissues used in medical devices can introduce several kinds of risks. The 1998 document primarily addressed geographical factors in the sourcing of the animal tissue. In addition to geographical factors, this document includes recommendations that recognize the role of careful animal husbandry to ensure safe tissue sources.

This guidance is intended to help you identify the possible risks related to tissues from animal sources when these tissues are used in medical devices.[1]

III. Scope

The information in this guidance is applicable to all medical devices that contain or are exposed to animal-derived materials (e.g., bovine, ovine, porcine, avian materials) with the exception of *in vitro* diagnostic devices. Consideration of these issues should aid in reducing the risk of infectious disease transmission by medical devices.

IV. Considerations When Using Animal-Derived Materials

A. Control of Animal Tissue Collection

FDA recommends you collect and document the following information for animal tissue-derived materials that are used as either device components (e.g., pericardium, viscera, bone, hyaluronic acid, collagen) or manufacturing reagents (e.g., tissue culture media, enzymes). You may document this information by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)) that contain this information. Information that is helpful during the review of animal-derived device materials includes Certificates of Analysis and Materials Safety Data Sheets, when available. Regulatory submissions and facility records (see 21 CFR 820.180) should describe the following:

- animal species;
- age of animal;
- specific tissue(s) used;
- animal country of origin and residence (more specific geographic location when appropriate);

- methods for monitoring the health of herd and the health of specific animals from which tissues are collected (e.g., vaccinations with live modified viruses that can co-purify in the desired tissue, active surveillance for human pathogens);
- the United States Department of Agriculture (USDA) status of the abattoir;
- methods and conditions for transporting animal tissue (e.g., tissue refrigeration and quarantine); and
- procedures for maintaining records on the above cited issues should be presented in regulatory submissions.

In addition, you should maintain records of the test results for any tests described above for each lot of material at the manufacturing facility and submitted in regulatory documents when appropriate.

B. Manufacturing Controls for Animal Tissue Components

FDA recommends you collect and document the information listed below for all animal-derived materials (and facilities) used in device manufacture. As stated previously, you may document this information by reference to other regulatory submissions (e.g., Master File, PMA, 510(k)) and Certificates of Analysis and Materials Safety Data Sheets, when available. Regulatory submissions and facility records (Device Master Record, see 21 CFR 820.181) should describe:

- test methods and release criteria permitting animal tissues to be further processed and/or combined with other animal tissue(s) or device components for manufacture;
- quarantine procedures for tissues until they have met/failed release criteria;
- test methods and acceptance criteria for assessing in-process and final product bioburden or sterility;
- methods for facility decontamination/sterilization so that cross-contamination is avoided; and
- procedures for maintaining records of the above cited issues should be provided in regulatory submissions.

You should maintain records of any test results for the tests described above for each lot of material at the manufacturing facility (see Device History Record (21 CFR 820.184)). When appropriate, you should also describe these results in regulatory submissions. In addition, you should demonstrate and validate manufacturing equipment cleaning, decontamination, and sterilization relative to the specific pathogen exposure, and document the results.

C. Sterilization

Because the issues for validating the sterilization of devices containing animal or human tissue are sufficiently complex to require a case by case assessment, we recommend you review the

FDA-recognized consensus standards listed in the References to this guidance.[2-8] Please note the extent of recognition of the current version of standards referenced in this document on the FDA web site in the database on Recognized Consensus Standards (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm). Enter the number of the Standard you wish to check into "Reference Number" field. In addition, we recommend you contact the FDA staff responsible for reviewing the specific device type to discuss your sterilization procedures.

When the risk to the public health is a virus that may be part of the animal tissue, we recommend that you consider the extent to which processing and sterilization inactivate or remove the virus. FDA recommendations for validating viral inactivation methods are described as follows:

Virus Validation Studies

You should assess the processing methods and sterilization techniques used in product manufacture for their ability to inactivate and remove viruses.Viral inactivation data are often obtained by determining the amount of virus in the unprocessed source material before and after exposure to production and sterilization processes.You may determine the extent to which viruses are inactivated using scaled down versions of the specific production and sterilization methods (e.g., acid extraction of collagen or dry heat sterilization) using appropriate model viruses. If you use a model virus during your viral inactivation study of your manufacturing and sterilization processes, you should document the relevance of the model virus you use to the actual virus present in the animal tissue (e.g., DNA-based or RNA-based, enveloped or non-enveloped).

The results of your viral inactivation studies should demonstrate that the sum of the log clearance of virus from the selected processing steps and sterilization processes are at least six logs greater than the concentration of virus anticipated in the unprocessed source material. While the design of viral clearance studies should take the specific product and manufacturing methods into consideration, insight into the general design of such studies is possible via review of the referenced guidance documents.[9,10] Viral inactivation studies do not address reduction of possible prion contamination.

D. Transmissible Spongiform Encephalopathy-Specific Issues

The Food and Drug Administration may issue rules specifically on Bovine Spongiform Encephalopathy (BSE) and the regulation of medical devices. Any final rule on BSE would take precedence over the recommendations of this guidance document. Current issues regarding BSE may be addressed at the following FDA website: http://www.fda.gov/animalveterinary/guidancecomplianceenforcement/complianceenforcement/bovinespongiformencephalopathy/default.htm

BSE is a degenerative disease that affects the central nervous system of cattle and is similar to other transmissible spongiform encephalopathies (TSEs) found in sheep (scrapie), deer

(chronic wasting disease),[11] and humans (Creutzfeldt-Jakob Disease or CJD). Current data suggest that the incubation period of 2 to 8 years after exposure is required before BSE symptoms are detectable. Currently, there are no treatments for TSE diseases and no screening tests for the detection of disease in a live animal or man. Diagnosis is achieved by post-mortem microscopic examination of brain tissue, as well as assays using ELISA and Western Blot techniques.

The BSE infectious agent is widely theorized to be a prion, (i.e., an abnormally folded form of a normal cellular protein) that facilitates the conversion of additional normal cellular proteins to the infectious prion structure (PrP(res)). Infectious PrP(res) has been detected in bovine brain, spinal cord, eye, ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary, adrenal, distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus.[12] The detection of TSE-infection in other tissues may occur in the future when data are available from more sensitive assays or larger animal studies. Transmission has been experimentally demonstrated in animal studies. [13] The TSE agent is also known to be extremely resistant to traditional forms of disinfection and sterilization.

Epidemiologic data suggest that the BSE epidemic in Great Britain began in 1986 by feeding cattle contaminated meat and bone meal as their protein source. According to the World Organization for Animal Health (OIE), as of 2011, 184619 BSE cases have been identified in Britain and twenty-two cases have been detected in North American cattle. As of 2011, there were also 221 definite or probable cases of new variant CJD (vCJD) worldwide, which is the human form of BSE that appears to be transmitted by consumption of BSE-tainted beef.[14] Since December 2003, four cases of Creutzfeldt-Jakob disease (vCJD) presumed to be transfusion-related vCJD have been reported.[15] Epidemiological data is updated periodically and is available at http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/CreutzfeldtJakobDisease/EpidemiologicalData/.

Given the long incubation time for disease onset, the absence of a screening test for live animals, and vCJD's fatal outcome, we recommend that you collect and document the following information for any material derived from an animal (e.g. cattle, sheep, goats, cervids such as deer and elk, etc.) with the potential to carry TSE infection:

- animal species;
- specific tissue used (if multiple tissues are used, identify all tissues used);
- animal's country of origin and country of residence (or a more specific geographic information when appropriate);
- methods for actively monitoring the health of herd and the health of specific animals from which tissues are collected;
- information concerning the long term health of the herd (e.g., documented breeding history, animal traceability, absence of TSE disease, and standard vaccinations such as live modified viruses which could co-purify in the desired tissue);

- the frequency and type of veterinarian inspections;
- animal feed composition (e.g., animal feed history records, including recordation of co-mingling of feeds, and, labeling of animal feed composition at distribution locations) (In 2008, FDA issued a rule prohibiting certain material from being fed to ruminants. The rule may be found at http://www.gpo.gov/fdsys/pkg/FR-2008-04-25/html/08-1180.htm);
- USDA status of the abattoir;
- animal age at sacrifice;
- animal sacrifice methods that reduce the risk of cross contaminating non-TSE tissues with material from tissues that could contain TSE;
- specifics of the pre and/or post mortem inspections (e.g., gross visual inspection, specific organs and anomalies exams, lab tests such as PrP testing);
- tests performed (and release criteria) for permitting tissue to be further processed and/or combined with other tissues and device components (e.g., a Certificate of Analysis); and
- methods for maintaining the records associated with the above cited issues should be provided in regulatory submissions.

You should maintain records of the test results for tests listed above for each lot of material at the manufacturing facility (see Device History Record (21 CFR 820.184)). When appropriate, you should also describe these results in regulatory submissions.

In addition, the residence time of TSE-infectious material on surfaces is unknown and methods to completely assure removal of TSE-infectious material from surfaces have yet to be fully understood. Products developed for use in abattoirs and non-manufacturing sites where surface contamination by materials from potentially TSE-infected animals (cattle, sheep, cervids such as deer and elk, etc.) may occur may not have been studied or validated for use on more critical sites or equipment such as those intended for the manufacture of devices from animal tissue. Therefore, in facilities involved in device manufacture using tissue from potentially TSE-infected animals (cattle, sheep, cervids such as deer and elk, etc.) your documentation should identify when/whether any potentially TSE-infected material may have been previously processed in your facility and what steps you have taken to address any potential contamination. This information could include the information previously discussed under "Manufacturing Controls for Animal Tissue Components" in section IV. B. of this guidance and the dates of previous tissue processing (see also 21 CFR 820.50).

Because screening assays that can ensure TSE-free bovine tissues have not been FDA-approved or introduced into general practice, the methods discussed above (e.g., monitoring animal feed, controlling animal husbandry and tissue handling) reflect the best available approaches for preparing safe medical devices from bovine tissue. However, when a TSE-screening assay is validated to accurately identify TSE-contaminated tissues, FDA will consider revising this guidance as appropriate and recommending that such a test be introduced into the standard operating procedures for bovine tissue collection and processing.

V. References

1. January 3, 2003 letter from David W. Feigal, MD to Manufacturers of FDA-Regulated Medical Devices Containing Animal Tissue Products or Components available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/4019B2_12.pdf

2. AAMI ANSI ISO 11135:2007 - Sterilization of health care products - Ethylene oxide - Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices

3. AAMI ANSI ISO 17665-1:2006 - Sterilization of health care products -- Moist heat -- Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices

4. AAMI ANSI ISO 11137-1:2006/(R) 2010 - Sterilization of health care products - Radiation - Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices

5. AAMI ANSI ISO 11737-1:2006 (R)2011 - Sterilization of medical devices - Microbiological methods Part 1: Determination of the population of microorganisms on product

6. AAMI ANSI ISO 11737-2:2009 - Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

7. AAMI ANSI ISO 14160:2011 - Sterilization of health care products - Liquid chemical sterilizing agents for single-use medical devices utilizing animal tissues and their derivatives - Requirements for characterization, development, validation and routine control of a sterilization process for medical devices

8. AAMI ANSI ISO 14937:2009 - Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation, and routine control of a sterilization process for medical devices

9. "ICH Viral Safety Document: QSA Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (63 FR 51074, September 24, 1998)" http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129101.pdf

10. "Viral Safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin" 35 USP <1050>

11. The web site for the USDA's Animal and Plant Health and Inspection Services concerning CWD (Chronic Wasting Disease) is

http://usdasearch.usda.gov/search?utf8=%E2%9C%93&affiliate=usda&query=CWD&commit=Search

12. WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies, http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

13. "Experimental interspecies transmission studies of the transmissible spongiform encephalopathies to cattle comparison to bovine spongiform encephalopathy in cattle" Cutlip, et.al., Journal of Veterinary Diagnostic Investigation **May 2011** vol. 23 no. 3 **407-420**

14. "Transmissible Spongiform Encephalopathies Advisory Committee Meeting Presentation: vCJD World Situation and Updates" by RG Will (August 1, 2011)

15. Incidence of variant Creutzfeldt-Jakob disease diagnoses and deaths in the UK compiled by N J Andrews at the Statistics Unit, Centre for Infections, Health Protection Agency. (updated 18th May 2011, http://www.cjd.ed.ac.uk/)